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REVIEW

Research progress on the roles of complement in liver injury

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Abstract

The complement system is crucial for maintaining immunological homeostasis in the liver, playing a significant role in both innate and adaptive immune responses. Dysregulation of this system is closely linked to the pathogenesis of various liver diseases. Modulating the complement system can affect the progression of these conditions. To provide insights into treating liver injury by targeting the regulation of the complement system, we conducted a comprehensive search of major biomedical databases, including MEDLINE, PubMed, EMBASE, and Web of Science, to identify articles on complement and liver injury and reviewed the functions and mechanisms of the complement system in liver injury.

Key Words: Complement system; Liver injury; Immune homeostasis; Pathogenesis; Review

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Core Tip: This review details the intricate relationship between the complement system and liver injury, highlighting its dual role in the pathology of liver injury. Although essential for immune response initiation, the complement system can also exacerbate liver injury. We synthesize current knowledge on the complement's involvement in liver injury, aiming to inform the creation of novel therapies that modulate this system to promote liver repair or halt disease progression. Future research directions and potential pharmaceutical targets are also discussed.

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INTRODUCTION

The complement system provides a vital link between the innate and adaptive immune systems[1]. Consisting of numerous proteins with enzymatic activity, this system is present in both serum and tissue fluid, and it forms an intricate protease cascade reaction network. Complement activation can be initiated by various triggers, including infections, ischemia-reperfusion events, and organ transplantation. This system has multiple functions crucial for maintaining internal environmental stability and defending against microbial invasion. The components of the complement system include intrinsic complement components, complement regulatory proteins, and complement receptors[2]. Additionally, given that the liver produces 80%-90% of plasma complement components, there is a significant interaction between the complement system and the liver. Thus, liver injury can markedly affect the release of complement factors, and imbalances in complement activation, whether excessive or insufficient, can impair liver function[3]. This review summarizes the role of the complement system in liver injury, offering references and directions for future research.

COMPOSITION OF THECOMPLEMENT SYSTEM

The complement system is an essential component of the human immune system, with most complement proteins being β-globulins. There are three pathways that can activate complement: The classical pathway (CP), the alternative pathway (AP), and the lectin route (LP). Although these pathways have different initiation stages, they all converge to produce the membrane attack complex (MAC). In the CP, activation is primary triggered by antigen-antibody complexes. Once the immune complexes are recognized by C1q, they bind to and activate C1r, and C1s, which then sequentially activate C4, C2, and C3, resulting in the formation of C5 convertase[4]. The AP plays a crucial role in situations in which antibodies are not yet available. The activation process of AP is independent of immune complexes, and it involves direct activation of C3 by microorganisms or exogenous foreign bodies. With the participation of factors B, D, and P, C3 and C5 convertases are formed to provide defense in the early stages of inflammation. By contrast, LP activation relies on triggering the mannose-binding lectin to recognize pathogens, resulting in a sequence of enzymatic cascade events that either cleave C4 and C2 to generate C5 convertase or cleave C3 directly to form C3 convertase[5].

The three aforementioned pathways can act synergistically and eventually converge at the terminal pathway, specifically at the C5 stage. During this stage, the products generated after C5 is cleaved by C5 convertase bind with C6-9 to form MAC, which plays a crucial role in lysing target cells or bacteria, activating inflammatory cells, and releasing inflammatory cytokines, thereby identifying and eliminating invading microorganisms. This cascading effect promotes the aggregation of immune cells at inflammation sites[6]. Moreover, among the complement activation products, C3a and C5a are the most potent inflammatory peptides, exhibiting a broad spectrum of functions. They act as strong chemoattractants for neutrophils and exhibit chemotactic activity for monocytes and macrophages. These peptides induce an oxidative burst, enhance phagocytosis, and promote the release of granule enzymes in neutrophils. They modulate cytokine expression in various cell types, reduce neutrophil apoptosis while enhancing thymocyte apoptosis, increase the expression of adhesion molecules on neutrophils, and activate the coagulation pathway[7]. Although these activation products are not necessarily the initiating factors in inflammatory disorders, they appear to be responsible for promoting and perpetuating inflammatory reactions. This process triggers acute inflammatory responses and promotes the release of pro-inflammatory mediators, further amplifying the immune response[8].

COMPLEMENT PRODUCTION

Hepatocytes and macrophages are the main cells responsible for complement production. Most serum complement components are secreted by hepatocytes, whereas macrophages are the main source of complement in inflammatory foci. In addition to hepatocytes and macrophages, other immune cells also contribute to the synthesis of certain complement components, particularly during inflammatory responses. Macrophages residing in the liver, known as Kupffer cells, constitute 80%-90% of the total macrophage population in the body. It is worth noting that, apart from the liver, other tissues in the body can also produce small amounts of complement, which is primarily related to the activity of macrophages within these tissues. Among the complement factors, C3 is the most abundant, and its concentration directly reflects the overall level of complement in the blood.

The production of complement is regulated by multiple factors, including inflammatory signals, infections, and specific immunoregulatory molecules. During acute inflammation or infection, the liver increases its production of complement to combat pathogens. Hormonal and cytokine influences, such as interleukin-6 (IL-6), can also promote complement synthesis. Therefore, the normal functioning of the complement system is crucial for maintaining effective immune defense mechanisms.

Patients with cirrhosis and liver failure exhibit significantly decreased serum complement levels, and this decline becomes more pronounced as the disease progresses[9]. This reduction leads to impaired immune function, weakened antigen-antibody reactions, and diminished phagocytic cell capabilities, making these patients more susceptible to various infections. This susceptibility further impairs liver function, creating a vicious cycle that exacerbates the condition.

COMPLEMENT SYSTEM AND LIVER HOMEOSTASIS

The liver performs critical functions such as metabolism, secretion, detoxification, and immune regulation. Because of its unique location and functions, the liver is highly susceptible to various types of damage. Liver injury has a complicated pathophysiology, mainly including direct hepatotoxic factors, immunological factors, metabolic factors, and viral infections[10]. Direct hepatotoxic factors such as drugs, alcohol, and chemotherapeutic drugs have direct damaging effects on hepatocytes[11]. Immunological factors involve autoimmune liver diseases (AILDs) and drug allergies that trigger immune responses[12,13]. Metabolic factors include fatty liver disease and damage caused by genetic metabolic factors[14]. Viral infection factors mainly include damage to the liver caused by hepatitis viruses or other non-hepatotropic viral infections[15]. The complement system protects the liver from infection and injury by enhancing the chemotaxis and phagocytosis of phagocytic cells, combating viruses, neutralizing toxins, lysing bacteria, and regulating immune responses. Several studies have demonstrated that C3 and C5a are essential for liver cell regeneration. Mice lacking C3 and C5 because of genetic knockout exhibit impaired liver regeneration[16,17]. However, an imbalance in the complement system can lead to the development and progression of liver injury.

Hepatocytes are the primary cells in the liver responsible for maintaining its morphology and function, and they are also the main targets of the complement system's impact on liver injury progression. Hepatocytes damage is the fundamental pathophysiological basis for various liver injury. The extent, rate, and quantity of hepatocyte damage, as well as their regeneration and repair status, are crucial intrinsic factors determining the severity of liver injury and its progression. Irreversible and repeated hepatocyte damage leads to disease progression[18]. Necrosis, apoptosis, necroptosis, and autophagy are typical types of hepatocyte death[19]. During the onset and development of various liver diseases, these different types of cell death are interrelated and can influence each other. Although they share some common pathways, they do not necessarily transform directly into one another, but rather, they contribute to the overall cellular response and disease progression.

THE ROLE OF THE COMPLEMENT SYSTEM IN LIVER INJURY

Complement system and hepatic inflammation

The liver is an organ with an abundant population of resident immune cells[20], and these cells in concert with bone marrow orchestrate immune responses. Within the human immune framework, activation of the complement system is meticulously regulated under normal physiological circumstances, mainly through local mechanisms to maintain liver homeostasis. This complex system causes hepatocyte damage through direct cytotoxicity and inflammatory mediator actions but protects hepatocytes by promoting the phagocytosis of pathogens by macrophages and clearing immune complexes. Therefore, the effects of the complement system on hepatocytes are multifaceted. When the liver is damaged or infected, the complement system is activated, producing a large number of inflammatory factors and complexes. These factors and complexes can further activate other immune cells, such as monocytes and endothelial cells, leading to an expanded and intensified inflammatory response. In particular, inappropriate or excessive activation of complement can exacerbate liver injury and enhance systemic inflammatory responses caused by sepsis and other factors. Hepatocytes exhibit notable resistance to activation by complement products, a characteristic linked to intricate intracellular signaling. Conversely, circulating complement C5a can activate liver endothelial cells and promote the expression of intercellular and vascular cell adhesion molecule 1 (VCAM-1), thereby stimulating neutrophils to enter liver sinusoids, releasing inflammatory mediators, and causing microcirculatory disturbances. It has been demonstrated that experimental C1 inhibitor therapy lowers VCAM-1 expression in the liver[21], whereas C3 deficiency and C3aR/C5aR blockers can inhibit the complement cascade reaction and prevent acute liver failure caused by systemic inflammation[22]. In animal models of *Escherichia coli* sepsis, inhibiting C3 or C5 can block MAC formation, reduce oxidative burst and leukocyte activation, lessen the release of systemic inflammatory mediators, prevent organ failure, and decrease mortality[23], verifying the negative consequences of high complement activation.

Immune complexes, and intestinal bacterial products including lipopolysaccharide (LPS) from gram-negative bacteria are all constant threats to the liver. Research has demonstrated that LPS activates Kupffer cells by binding to Toll-like receptor 4 (TLR4), thereby inducing the production of inflammatory cytokines such as IL-1 and tumor necrosis factor alpha (TNF-α) and mediating liver injury[24]. The complement system plays a pivotal role in safeguarding the liver from these threats through several mechanisms; specifically, it enhances phagocytosis, thereby promoting the clearance of invading intestinal bacteria and their toxins by macrophages and neutrophils and reducing their entry into the liver[25], forms membrane attack complexes to directly kill or lyse bacteria, preventing their spread within the liver[26], attracts immune cells to the site of infection to help clear pathogens[27], binds to immunocomplexes, facilitating their removal and alleviating liver burden, maintains the integrity of liver endothelial cells, blocking the entry of bacteria and toxins into the liver through the bloodstream, regulates immune tolerance, averting excessive immune responses that could

damage the liver, and directly inhibits the growth and reproduction of certain pathogens, diminishing their threat to the liver. As an integral part of the innate immune system, the complement system quickly responds to invasion by intestinal bacteria, serving as a first line of defense and shielding the liver from damage. Consequently, conducting in-depth research on the relationship between the complement system and liver inflammation and employing specific complement modulators or gene therapy to repair or inhibit genes causing abnormal complement activation while preserving its beneficial function in liver homeostasis might represent a viable strategy for treating liver inflammatory diseases.

Complement system dysregulation in alcoholic liver disease pathogenesis

Alcoholic liver disease (ALD) is common, with both acute and chronic alcohol-induced injuries affecting liver regeneration[28]. This mechanism involves an increase in reactive oxygen species production during ethanol metabolism, leading to antioxidant depletion and lipid peroxidation in the liver, which triggers oxidative stress, inflammatory responses, and lipid metabolism disorders, ultimately leading to further disease progression[29]. In ALD, the complement system plays a significant role in the development of alcoholic hepatitis (AH), alcoholic liver fibrosis, and cirrhosis[30]. Studies indicated that the intermediate products of alcohol metabolism can activate the complement cascade reaction on liver membranes**.** Therefore**,** alcohol intake can lead to activation of the complement system, triggering a series of inflammatory responses and immune damage, further exacerbating liver injury and disease progression. Alcohol itself can directly bind to complement proteins, thereby activating them. It might also induce inflammation or cause hepatic cell damage, triggering an immune response from the complement system.

In patients with ALD, the levels of complement components (such as C3 and C4) are usually elevated at both the serum and hepatic levels. These changes are related to the activation of the complement system, and they reflect the extent of liver damage and inflammation. Specifically, an increase in serum C3 Levels can indicate the progression and worsening of ALD[31]. Research has found that ethanol in the diet can cause significant fatty degeneration in the liver of normal mice and increase the content of triglycerides in the liver. Mice lacking C3 display resistance to or marked mitigation of acute or chronic liver steatosis induced by alcohol[32]. In a separate animal investigation, it was discovered that the complement regulatory protein decay-accelerating factor (CD55/DAF) functions to inhibit C3 and C5 activation, alleviate liver inflammation caused by inflammatory factors such as TNF-α, reduce triglyceride accumulation, and delay the progression of ALD. Conversely, the depletion of C3 has been found to offer a degree of protection against alcohol-induced hepatic steatosis[33]. Moreover, studies have found that the C3 activation product C3a is essential for the development of hepatic steatosis. Through the regulation of glycine transfer RNA (Gly-tRF) expression by cytochrome P450 2E1, modulating Gly-tRF expression promotes intrahepatic lipid deposition through C3 activation complement products. C3 activation inhibitors or Gly-tRF blockers could represent precise and potential treatments for alcohol-induced fatty liver disease (AFLD)[34].

Early research discovered that acetaldehyde could bind to the hepatocyte plasma membrane, activating C3 by inducing structural changes on the surface of the plasma membrane. It was found that the levels of C1, C3, and C8 were increased by long-term alcohol consumption. Serum C3a levels are linked to liver damage and hepatic steatosis in long-term alcohol consumers. In an *in vivo* model of ethanol feeding, AFLD occurred in wild-type C3 mice, whereas mice with C3 gene depletion did not develop AFLD. By contrast, $C3^{-/-}$ mice specifically exhibited increased adiponectin levels in both serum and liver but decreased transcripts of lipogenic enzymes, adiponectin receptor 2, and adipose differentiation-related protein[35]. Conversely, C5-deficient mice exhibited opposite phenotypes from C3-deficient mice. Another study found that the livers of C5-deficient mice featured more cholesterol deposits[36]. These findings imply that C3 and C5 contribute differently to the development of AFLD. However, the mechanisms have not been fully verified.

Unlike AFLD, AH involves both the accumulation of triglycerides in hepatocytes and inflammation mediated by liver dysfunction. Inflammatory cytokines and the complement system contribute significantly to the development of AH[37,38]. Studies have reported that ethanol activates the classical complement pathway by binding to apoptotic liver cells *via* C1q and induces the expression of TNF-α and IL-6, mediating liver injury. Therefore, C1q deficiency is associated with reduced inflammatory cytokine expression and alleviated liver damage[39]. Another animal study also confirmed these findings[40]. Moreover, in patients with AH, increased C5 and C5aR levels are major characteristics of sustained inflammation[41,42]. The underlying mechanism might involve crosstalk of TLRs/nuclear factor kappa B signaling pathway with C3aR and C5aR in AH[43,44]. Additionally, factor D, a component of the complement AP, can alleviate ethanol-induced inflammation and hepatocyte apoptosis through amplification in a dependent manner, promoting hepatic healing and recovery in AH[45]. Therefore, complement activation is anticipated to emerge as a prognostic and diagnostic marker for patients with AH[46].

Chronic liver injury and abnormal repair processes caused by long-term exposure to alcohol lead to the development of alcoholic hepatic fibrosis, damaging the liver's structure and eventually progressing to cirrhosis. Numerous studies have confirmed that the complement system is involved in the development of alcoholic liver fibrosis and cirrhosis. Blockade of C5aR1 alleviated liver inflammation and fibrosis in a mouse model of non-alcoholic steatohepatitis (NASH) by regulating TLR4 signaling and macrophage polarization[47]. C4a, in combination with ceruloplasmin, fibrinogen-alpha and paraoxonase/arylesterase 1, serves as an indicators of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected alcoholic patients with cirrhosis[48]. The underlying mechanism might be related to decreased synthesis and excessive depletion of complements following alcoholic exposure.

In summary, within the context of ALD, serum complement levels are typically elevated in the early stages, but they often decrease during fibrosis and cirrhosis. This inconsistency complicates the use of complement for assessing the progression of ALD. Consequently, further experimental and clinical studies are needed to elucidate the relationship between the complement system and ALD and to explore potential therapeutic targets. For patients with ALD, avoiding excessive alcohol consumption is a crucial measure to prevent disease progression. At the same time, timely treatment and intervention for the already damaged liver are also very important.

Association of complement components in metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), also known as nonalcoholic fatty liver disease (NAFLD) or metabolic-associated fatty liver disease, is fundamentally characterized by excessive lipid accumulation within the hepatocytes[49]. With the global rise in obesity and diabetes, its incidence has been increasing. MASLD can progress from simple fatty liver to metabolic dysfunction-related steatohepatitis, liver fibrosis, cirrhosis, and even HCC [50]. The complement system is involved throughout the development of hepatic lipid deposition and is closely associated with the risk of MASLD/NAFLD. However, the relationship between the various components of the complement system and the risk and severity of MASLD/NAFLD is not consistent.

In a cross-sectional study conducted in China, 7540 participants were included. The study found that serum complement C3 levels were positively correlated with the prevalence and severity of NAFLD, and this association was unrelated to obesity and metabolic syndrome[51]. The complement system is widely activated in patients with NAFLD, with deposits of activated C3 and C4d observed in liver tissue. In most C3-positive livers, there is accumulation of C1q and mannan-binding lectin (MBL), and 50% of C3-positive liver tissues exhibit deposits of MAC-related C9. Complement factor deposits are primarily observed around hepatocytes with macrovesicular steatosis. Patients with activated C3 deposits exhibit more significant neutrophil infiltration in the liver[52]. Another study found that patients with NASH have a significantly higher rate of hepatic C3 activation and decreased levels of H factor (an AP negative regulator), whereas the deposits of P factor (C convertase stabilizer) and C3c (a product of C3a activation) are positively correlated with the degree of hepatic inflammation[53]. Animal experiments revealed that wild mice fed a high-fat diet exhibit elevated serum C3 and C5. Compared with wild mice, $C5^{-/-}$ mice display reduced hepatic fat degeneration and lower levels of inflammatory factors[54].

The prevalence of NAFLD in adults is independently linked to higher serum C3 Levels[55]. C1q is implicated in the occurrence and development of HCC through activation of the collagen receptor discoidin domain receptor 1, revealing another mechanism by which the complement system contributes to the development of HCC[56]. Therefore, targeting the inhibition of the complement AP to delay the progression of non-alcoholic steatohepatitis and associated HCC is a potential therapeutic strategy. A meta-analysis indicated that increased levels of complement components, including C3, C5, complement factor B, and acylation stimulating protein, are associated with an increased risk and severity of NAFLD [57]. A Mendelian randomization analysis also found a significant association between elevated C3 Levels and an increased risk of NAFLD[58]. These results indicate that MASLD presents a chronic inflammatory state, in which elevated levels of inflammatory factors and activation of the complement system during hepatic fat degeneration promote an amplified inflammatory response. This in turn exacerbates lipid accumulation within hepatocytes. Specifically, elevated C3 Levels are identified as an independent risk factor for the occurrence and development of MASLD; moreover, inhibiting the alternative complement pathway may represent a potential therapeutic strategy to slow disease progression.

Complement and viral hepatitis

Hepatotropic virus infections can induce liver inflammation, termed viral hepatitis. Chronic viral hepatitis increases the risks of cirrhosis and HCC[59]. Although the specific pathogenesis is not fully understood, the continuous immune system response and the damage it causes play crucial roles in this process[60]. This suggests that immunomodulation has significant potential in the prevention and treatment of these diseases.

HCV-infected patients exhibit lower serum C4 Levels than healthy controls, and reduced C4 mRNA levels in liver tissue are associated with the severity of liver inflammation[61]. Further research indicates that the HCV core gene can inhibit C4 activation[62]. Additionally, HCV proteins can suppress the synthesis of complement C3 by decreasing the activity of C3 promoter, resulting in significantly lower serum C3 Levels and C3 mRNA expression in liver tissues of patients with HCV compared with the findings in healthy individuals[63]. In patients with chronic HCV infection, higher serum concentrations of C3, C4, and MBL are positively correlated with responses at the end of treatment[64,65]. Moreover, the stage of hepatic fibrosis is related to the reduction of complement components such as C3, C4, and H[66]. Reports indicate that low levels of C4a are associated with severe hepatic fibrosis in children with chronic hepatitis C (CHC)[67]. Another study found that the levels of C3a were significantly elevated in patients with HCV-related HCC[68]. Some HCV forms express complement regulatory protein CD59 on their surface, which inhibits the formation of MAC, allowing the virus to evade the complement system's attack; loss of CD59 function enhances complement-mediated destruction of HCV[69]. Research has found that patients with CHC exhibit decreased CH50 activity and increased formation of the sC5b-9 complex, which is associated with hepatocyte necrosis and inflammatory activity[70]. Complement C1q is primarily produced by cells including Kupffer cells, and it forms a complex with apolipoprotein E (ApoE). Research has found that in viral hepatitis and NAFLD, immune cells accumulate in the liver, activating the complement cascade reaction and producing a large number of C1q-ApoE complexes. These serve as new pathological biomarkers for viral hepatitis B and C, as well as NAFLD[71]. These research results indicate that the complement system can act as a biomarker for viral hepatitis diagnosis and assessment.

In hepatitis B virus (HBV)-infected individuals, the haplotype frequency of the MBL gene's exons and promoter region is significantly increased, whereas serum MBL levels are markedly decreased[72], suggesting that MBL can protect against HBV infection to some extent. In patients with HBV and elevated transaminases, serum C4 levels have a certain predictive value for liver biopsy results[73]. In studies of HBV-related acute-on-chronic liver failure (HBV-ACLF), complement activation is inhibited, the formation of C1q is significantly reduced, the CP recognition molecule C1q was identified as significant in the pathogenesis of HBV-ACLF[74]. Additionally, research has discovered that C3 and C3a levels could potentially serve as new biomarkers for predicting the prognosis of HBV-ACLF. Furthermore, both transgenic experimental animals carrying HBV and patients with chronic HBV infection exhibit reduced levels of the

complement regulatory protein CD59 within the liver[75], which increases hepatocyte sensitivity to complement, ultimately leading to chronic HBV infection[76]. Therefore, inhibiting the HBc-CD59 interaction can prevent inflammation-induced liver damage caused by HBV infection, and blocking this process represents a potential approach to treating inflammatory liver damage.

Additionally, the serum C5a concentration in patients with CHB is significantly elevated. *In vitro* experiments revealed that C5a can stimulate hepatic stellate cells (HSCs) and increase hyaluronic acid and type IV collagen levels. The increase in C5a content can inhibit the TNF-α-induced apoptosis of HSCs. These findings highlight the potential role of C5a in the regulation of liver fibrosis[77]. However, another study found that serum C5a levels in patients with chronic HBV infection are negatively correlated with liver fibrosis staging, significantly decreasing in severe fibrosis stages and early cirrhosis[9]. This might be related to reduced C5 synthesis by hepatocytes or enrichment of circulating C5 within the liver. These findings bring confusion to evaluating the condition of HBV-infected patients through serum C5 Levels, requiring analysis based on the specific circumstances of the patient. High C5a levels promote inflammation and fibrosis, but they can also indicate relatively preserved synthetic function of hepatocytes.

Complement and chemical liver injury

Liver function impairment caused by hepatotoxic substances is termed chemical liver injury. Carbon tetrachloride (CCl_4) is commonly used to induce acute or chronic liver damage for establishing animal models of liver injury[78]. Similarly, studies illustrated that the complement system also contributes to liver repair and regeneration following chemical liver injury[79]. C3 deficiency impairs liver regeneration following CCl_4-induced liver damage in mice, which leads to delayed clearance of apoptotic and necrotic cells. C3a supplementation has been found to restore liver regeneration[80]. Therefore, C3, C5, C3a, and C5a play a role in regulating liver regeneration after toxic injury. By contrast, the targeted inhibition of complement activation through the use of a C2-FH inhibitor has been demonstrated to protect against acetaminophen-induced liver injury in mice[81]. These findings suggest that although the complement system plays a role in the pathogenesis of chemical liver injury, it also has an important function in the regeneration process following liver injury.

Complement and AILD

The liver, which commonly encounters intestinal bacterial products, has a special immunological tolerance. Without immunological tolerance, the liver would constantly be inflamed[82]. Rejection reactions are less frequent after liver transplantation than after kidney or heart transplantation[83]. Moreover, transplanted livers can also induce partial tolerance in the recipients of other transplanted organs[84]. Despite this, the liver can sometimes be mistakenly attacked by its own immune system, resulting in AILDs. AILDs encompass a spectrum of conditions including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis, and their overlap syndromes. These disorders are frequently associated with other autoimmune diseases, underscoring the intimate relationship between their pathogenesis and immune system dysregulation. Some studies have reported elevated levels of plasma C3 in both patients and animal models with AIH[85]. A proportion of pediatric patients with AIH exhibit C4d deposition[86,87]. Studies on adult patients with type I AIH revealed increased levels of complement C3 and C4[88]. In AIH model mice, preemptive administration of cobra venom factor to neutralize complement or treatment with DAF can alleviate liver injury. This suggests that the complement system is excessively activated in AIH[89]. PBC, known as primary biliary cirrhosis, is characterized by anti-mitochondrial antibody positivity and elevated serum IgM levels[90]. Abnormal levels of complement components C3 and C4 are observed to varying degrees, suggesting that humoral immunity plays a role in the onset and progression of PBC. Although plasma C3 and C4 Levels are elevated in patients with PBC, they do not significantly contribute to bile duct cell damage. Bile duct narrowing is a symptom of the progressive illness primary sclerosing cholangitis. Elevated plasma C3 levels have been identified, and this finding might possibly be related to inflammation triggered by bile duct stones[91]. However, another study observed no deposition of C3d and C5b9 in the bile ducts on immunohistochemistry[92]. Reduced levels of circulating complement factor H are correlated with heightened disease severity and an elevated rate of relapse in patients with AIH[93].

Complement and hepatic ischemia-reperfusion injury

Hepatic ischemia-reperfusion injury (IRI) can occur in situations such as liver trauma, resection, and transplantation, resulting from an ischemic cascade reaction. The complement system plays a role in mediating hepatic IRI and regulating liver regeneration[94]. Changes in the biomarkers of complement activation (C3a, C5a, and sC5b-9) could serve as prognostic indicators for survival or rejection after liver transplantation[95]. Research indicates that C1q expression might play a primary role in liver IR injury, especially during the early stages of perfusion[96]. A deficiency of MAC can protect liver from the harmful effects of IRI[97]. Thus, inhibiting the complement cascade reaction could be a new treatment strategy for IRI. Furthermore, steatosis increases the liver's vulnerability to IRI, with C3 playing a crucial role in this process[98]. The therapeutic application of soluble complement receptors type 1 can effectively inhibit complement activation, thereby improving microvascular circulation and reducing the number of adherent leukocytes[99]. In rats with partial hepatic IRI, treatment with a C5aR blocker significantly reduced the levels of liver enzyme markers serum and tissue inflammatory factors. This also slowed liver tissue pathology, revealing the key role of C5a in liver IRI[100]. In similar experiments, the use of the complement system inhibitor CR2-CD59 to block complement activation also demonstrated significant efficacy in a mouse model of IRI[101]. Unlike other currently available complement inhibitors, CR2-CD59 is a promising non-toxic treatment approach that can protect the liver from damage and promote regeneration in various clinical settings[102].

Properdin, as a regulator of the complement system, stabilizes C3 convertase, thereby enhancing the formation of activation products in both the classical and APs. Inhibition of properdin can significantly improve hepatic IRI by

inhibiting the cleavage and activation of C3 and C5[103]. Anti-C5 antibodies significantly improve hepatic IRI primarily by inhibiting the C5a-mediated inflammatory cascade. This both suppresses platelet aggregation in the early stages and reduces the activation of infiltrating macrophages/neutrophils and hepatocyte apoptosis during the later reperfusion phase. Given its efficacy, clinical availability, and controllability, C5-targeted intervention might offer a novel therapeutic strategy for hepatic IRI[104,105].

CONCLUSION

The complement system plays a crucial role in immune inflammatory responses and regulates liver cell function, exhibiting a dual role in liver injury (Table 1). However, this might lead to the neglect of its positive contributions to maintaining liver homeostasis. Although complement as a non-invasive biomarker for liver diseases is a popular research area, most studies are still in the early stages, requiring further research and validation before it can be used as a biomarker, diagnostic tool, and prognostic indicator. Because of various factors influencing serum complement levels, including the etiology and severity of liver disease, levels of complement factors, and redistribution of complement within the liver or circulation, no complement marker has been identified that can accurately predict the progression of liver disease. Additionally, despite extensive basic and clinical research indicating a close relationship between complement and liver disease progression, there is a lack of drugs targeting complement regulation in the treatment of liver diseases. Therefore, it is necessary to conduct in-depth research on the role of the complement system in liver injury. Comprehensive assessment of its dual role and dynamic characteristics in liver diseases, along with exploring its specific mechanisms in liver injury progression, will facilitate better targeting of the complement system for accurate diagnosis and precise treatment of liver diseases.

Table 1 Complement-associated liver injury

Disease	Complement	Function	Ref.
Hepatic inflammation	C1 inhibitor	Reduce the interaction between white blood cells and endothelial cells in the liver and the expression of VCAM-1	[21]
	C3 deficiency and C3aR/C5aR blockers	Inhibit the complement cascade reaction and reduce liver inflammation	[22]
	Inhibiting C3 or C5	Reduce the 'oxidative burst' induced by bacteria and leukocyte activation, decrease the release of systemic inflammatory mediators	[23]
Alcoholic liver disease	Lacking or inhibit C3, CD55/DAF	Reduce triglyceride accumulation, alleviate liver inflammation caused by inflammatory factors such as TNF-α	[32,33]
	C3a	Upregulating the expression of Gly-tRNA can promote hepatic steatosis	[34]
	C3	Complement factor C3 and lipid regulators have significant interactions in ethanol-induced steatosis	[35]
	C5-deficient	Increased cholesterol deposition in the liver	[36]
Alcoholic hepatitis	C1q	Ethanol activates the classical complement pathway by binding to apoptotic liver cells *via* C1q, and induces the expression of Tumor Necrosis Factor-alpha and Interleukin-6	[39,40]
	C5aR	Involving the regulation of pro-inflammatory responses by the TLRs/NF-κB signaling pathway	[41-44]
	Factor D	By activating the complement alternative pathway and amplifying in a dependent manner, it alleviates ethanol-induced inflammation and hepatocyte apoptosis	[45,46]
	Inhibition C5aR1	Regulating TLR4 signaling and macrophage polarization	[47]
MASLD/NAFLD	C3	It involves the activation of the complement classical pathway and lectin pathway, mediating neutrophil infiltration	[52,53]
	Lacking C5	Reduced hepatic fat degeneration and lower levels of inflammatory factors	[54]
	C1q	Implicated in the occurrence and development of HCC through activation of the collagen receptor discoidin domain receptor 1	[56]
Viral hepatitis type C	C4	The HCV core gene can inhibit C4 activation	[62]

	C3	HCV proteins can suppress the synthesis of complement C3	[63]
	CD59	Inhibits the formation of MAC, helping the virus to evade the complement system's attack	[69]
	CH50	Promote the increase in MAC formation	[70]
	C1q	Immune cells accumulate in the liver, activating the complement cascade reaction and producing a large number of C1q–ApoE complexes	[71]
Viral hepatitis type B	MBL	The haplotype frequency of the MBL gene's exons and promoter region is significantly increased	[72]
	C4, C1q	Complement activation is inhibited, and the formation of C1q is significantly reduced in HBV-ACLF	[73,74]
	CD59	Downregulation of CD59 increases hepatocyte sensitivity to complement-mediated cytotoxicity	[75,76]
	C5a	Inhibit tumor necrosis factor-induced apoptosis of HSCs and participate in liver fibrosis	[9,77]
Chemical liver injury	C3, C3a	Clear apoptotic and necrotic cells and promote the proliferation and regeneration of liver cells	[80]
	C2-FH inhibitor	Inhibition of complement activation can attenuate acetaminophen-induced liver injury in mice	[81]
Autoimmune liver disease	C3	It is related to the pathogenesis of autoimmune liver diseases	[85]
	C4	Participate in autoimmune hepatitis	[86,87]
	DAF, CVF	Inhibit liver injury mediated by excessive complement activation	[89]
	Factor H	Participate in the recurrence and progression of autoimmune hepatitis	[93]
Hepatic IRI	C3a, C5a, and sC5b-9	Play different roles at different time points after liver transplantation	[95]
	C1q	Liver injury caused by increased oxidative stress	[96]
	C6	Locally inhibit the formation of MAC, reduce the expression of inflammatory mediators, and enhance anti-apoptosis	[97]
	sCR1	Improving microvascular circulation and reducing the number of adherent leukocytes	[99]
	C5aR blocker	Reduced the levels of liver enzyme markers serum and tissue inflammatory factors	[100]
	CR2-CD59	Inhibit complement activation and promote liver regeneration.	[101,102]
	Properdin	Improve hepatic IRI by inhibiting the cleavage and activation of C3 and C5	[103]

ACLF: Acute-on-chronic liver failure; CVF: Cobra venom factor; DAF: Decay-accelerating factor; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HSCs: Hepatic stellate cells; IRI: Ischemia–reperfusion injury; MASLD: Metabolic dysfunction-associated steatotic liver disease; MAC: Membrane attack complex; NAFLD: Nonalcoholic fatty liver disease; NF-κB: Nuclear factor kappa B; sCR1: Soluble complement receptors type 1; TLR: Toll-like receptor; TNF-α: Tumor necrosis factor-α; VCAM-1: Vascular cell adhesion molecule 1.

FOOTNOTES

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